Correlation between computed tomographic findings, bronchioloalveolar carcinoma component, and biologic behavior of small-sized lung adenocarcinomas

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Objective: Differentiation of bronchioloalveolar carcinoma from other subtypes of lung adenocarcinomas is important in the preoperative assessment of patients. We examined the biologic aggressiveness of small-sized adenocarcinomas according to the pathologically defined bronchioloalveolar carcinoma degree and its correlation with computed tomography findings. In addition, we attempted to predict which patients were suitable for a lesser resection.

Methods: Of 424 consecutive patients who underwent operation for primary lung cancer in the last 3 years, 114 with a histopathologically proven adenocarcinoma 3 cm or less in diameter underwent complete removal of the primary tumor. We examined the characteristics of patients classified into 3 groups based on the proportion of the bronchioloalveolar carcinoma component: 0% to 20% (n = 40), 21% to 50% (n = 38), and 51% to 100% (n = 36). We also investigated the correlation of the bronchioloalveolar carcinoma component with computed tomography findings such as ground-glass opacity (defined as a hazy increase on the lung window) and tumor shadow disappearance rate (defined as the ratio of the tumor area of the mediastinal window to that of the lung window).

Results: Male gender ($P = .0001$), advanced pathologic stage ($P = .001$), larger size of the tumor ($P = .004$), nodal involvement ($P = .04$), pleural invasion ($P = .0003$), lymphatic invasion ($P = .002$), and vascular invasion ($P = .0002$) were observed more often among patients with a smaller proportion of bronchioloalveolar carcinoma. A positive and significant correlation was found between the rate of bronchioloalveolar carcinoma component and ground-glass opacity ($R^2 = 0.488$, $P < .0001$) and tumor shadow disappearance rate ($R^2 = 0.727$, $P < .0001$). As an independent predictor of nodal status, tumor shadow disappearance rate ($P = .015$) and bronchioloalveolar carcinoma component ($P = .015$), as well as tumor size, were significantly valuable, although ground-glass opacity proportion ($P = .086$) was marginally informative.

Conclusions: Small-sized adenocarcinomas with a greater ratio of bronchioloalveolar carcinoma component showed less aggressive behavior. Both tumor shadow disappearance rate and ground-glass opacity ratios, which are obtained preoperatively, were well associated with bronchioloalveolar carcinoma ratios, which are determined postoperatively. Furthermore, tumor shadow disappearance rate had a stronger impact as a predictor of bronchioloalveolar carcinoma component. Preoperative assessment of tumor shadow disappearance rate may be useful to identify patients requiring a less extensive pulmonary resection.

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The extensive use of computed tomography (CT) scanning for early detection of lung cancer is confronting our approach to surgery. However, there are no definite criteria regarding CT findings that characterize early lung cancers or determine the clinical and tumor biology preoperatively. The increasing number of patients with small-sized lung cancers has led to doubts about whether some of these cancers can be treated with a lesser resection, despite much controversy surrounding the effectiveness of lesser resection as an alternative to lobectomy.[1-6] Approximately one fifth of clinical T1 cancers are linked to nodal involvement,[1,5,7] and the rest have a more inactive biologic performance that should be defined as early cancers. The risks of nodal involvement and subsequent systemic metastases are not completely associated with the size of the tumor. The capacity to differentiate which of these small cancers would have an active or inactive biologic performance is remarkably crucial. Diagnosis of lung cancers at an early stage is important because eradication of small-sized tumors can be accomplished with less loss of tissue. This results in reduced operative complications and loss of pulmonary function. In addition, the procedure is associated with longer survival, and if another tumor is found, the patient would be in better condition to resist a second resection of tissues. The larger the extent of the initial resection, the more restricted the surgical choice for potential subsequent resections.

Ground-glass opacity (GGO), termed as a misty and obscure component in lung attenuation on high-resolution CT (HRCT), seems linked to tumor biology and thereby to the risk of nodal involvement. In particular, cancers 2 cm or smaller, in which the ratio of GGO relative to the whole shadow of the tumor is 50% or greater, are bronchioloalveolar carcinomas (BACs) without nodal involvement.[8-10] In addition, BAC may stand for the preinvasive type of adenocarcinoma often seen at the margin of invasive adenocarcinoma.[1-14] From these findings, we speculated that limited lung resection might be an acceptable approach to the treatment of small BACs. In addition, Takamochi and colleagues[15] proposed a radiologic parameter, namely, the tumor shadow disappearance rate (TDR), designed from tumor shadows on both pulmonary and mediastinal window setting images on CT, as a predictor of N0 disease in patients with an adenocarcinoma. BACs typified by a lepidic growth pattern along the alveoli without invasive areas have an inactive performance and are usually expressed as GGO or tumor shadow disappearance areas on CT. Consequently, the CT characteristics (ie, GGO and TDR) of the tumors must be identified. Notably, the features of these different entities need to be well defined and correlated with preoperative imaging findings and clinical outcomes. Understanding the biologic performance of these small lung cancers preoperatively could also provide clues in selecting patients for limited pulmonary resection. Therefore, we examined the aggressiveness of small-sized pulmonary adenocarcinomas according to the proportion of BAC increase and correlated the proportion of GGO and TDR calculated on the preoperative HRCT with that of BAC components defined on sections of surgical specimens postoperatively. The results of this study can improve our approach to diagnosing and treating small lung adenocarcinomas, which may become an ever more vital portion of thoracic surgical tradition.

Patients and Methods

From January 2000 to December 2002, 424 consecutive patients underwent operation for primary lung cancer with the same surgical team. Of these patients, 114 with a pathologically proven adenocarcinoma 3 cm or less in diameter underwent complete removal of the primary tumor together with ipsilateral hilar and mediastinal lymph nodes. Surgical-pathologic staging was performed according to the New International Staging System for Lung Cancer.[16] This retrospective chart review at our institution was considered exempt research.

Contrast-enhanced HRCT was performed on an Asteion (Toshiba Medical Systems, Tokyo, Japan). All slices with 6-mm spacing were obtained from the apex of the lung to the base. In addition, slices with 2-mm spacing were taken through the nodule. The images were photographed using a window level of −600 Hounsfield units (HU) with a window width of 1700 HU (lung windows) and a level of 25 HU with a width of 350 HU (mediastinal windows). All lesions were completely resected within 1 month after CT. TDR and GGO were assessed by independent observers, and discrepancies in evaluation among the observers were resolved by averaging the values determined by them. The observers quantified the maximum dimension of the tumor (maxD) and the largest dimension perpendicular to the maximum axis (perD) on both the lung and mediastinal windows. As previously reported,[15] TDR was defined as follows:

$$\text{TDR (\%)} = \left(1 - \frac{\text{maxD} \times \text{perD on mediastinal windows}}{\text{maxD} \times \text{perD on lung windows}}\right) \times 100$$

The tumors resected surgically were fixed in 10% formalin and embedded in paraffin. The sections including the largest cut were stained with hematoxylin-eosin and elastica van Gieson, and examined histopathologically. Patients were classified into three groups according to the proportion of BAC area relative to the whole tumor, namely, tumors in which the BAC proportion comprised 0% to 20%, 21% to 50%, or 51% to 100%. These estimations were performed by independent pathologists in the same manner as that for CT reviews. The cutoffs of BAC proportion were chosen so that an approximately equal number of patients whose tumors had a low, medium, or high proportion of BAC component were included in each group.

The clinical records of all patients were reviewed for age, sex, pathologic stage, tumor size (T factor), lymph node status (N factor), pleural involvement (P factor), lymphatic invasion (Ly factor), and vascular invasion (V factor). P factors were defined as follows: P0, visceral pleura is not involved by tumor; Pl, tumor has

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TABLE 1. Clinicopathologic characteristics of patients with lung adenocarcinoma 3 cm or less in diameter in relation to proportion of pathologic BAC

Factors	Overall	Pathologic BAC 0%-20%	Pathologic BAC 21%-50%	Pathologic BAC 51%-100%	*P* value
No. of patients	114	40	38	36	
Age, y (mean, range)	64 (39-81)	65 (48-80)	62 (39-81)	64 (40-81)	.2927
Sex					
Male	52	28	18	6	.0001
Female	62	12	20	30	
Pathologic stage					
I	92	26	31	35	.0011
II	8	3	4	1	
III	12	9	3	0	
IV	2	2	0	0	
T factor					
T1	91	27	29	35	.0035
T2	13	5	7	1	
T3	3	3	0	0	
T4	7	5	2	0	
N factor					
N0	98	31	32	35	.0377
N1	8	3	4	1	
N2	8	6	2	0	
P factor					
P0	75	19	24	32	.0003
P1	25	12	9	4	
P2	10	5	5	0	
P3	4	4	0	0	
Ly factor					
Ly (−)	87	25	27	35	.0015
Ly (+)	27	15	11	1	
V factor					
V (−)	90	24	30	36	.0002
V (+)	24	16	8	0	

BAC, Bronchioloalveolar carcinoma.

reached but not invaded the visceral pleura; P2, tumor has invaded the visceral pleura but does not involve the parietal pleura; and P3, tumor has invaded the parietal pleura or the chest wall. In the case of lymphatic and vascular invasion, adenocarcinoma cells were identifiable in the lymphatic and blood vessel lumen, respectively.

The Kruskal-Wallis rank test was performed to investigate the associations between the proportion of BAC component and clinicopathologic factors. We also examined which TDR or GGO ratio correlated more closely with the BAC ratio using a correlation coefficient. To further elucidate the independent variables in relation to the prediction of nodal involvement, we performed multiple logistic regression analyses as multivariate models in which we used categories for sex and continuous variables for age, tumor size, BAC ratio, GGO ratio, and TDR.

Results

The clinicopathologic findings of the patients are summarized in Table 1. Of 114 patients, 52 (46%) were men and 62 were women. The mean age was 64 years (range 39-81 years). The pathologic examination showed stage I disease in 92 patients (81%), stage II in 8 patients, stage III in 12 patients, and stage IV in 2 patients. The two patients with stage IV disease had pulmonary metastases in the other lobe and brain metastasis. T1 and P0 tumors were found in 91 patients (80%) and 75 patients (66%), respectively. Ninety-eight patients (86%) had no nodal involvement, whereas hilar and mediastinal lymph node involvement was discovered in 8 patients (7%). Lymphatic and vascular invasion occurred in 27 patients (24%) and 24 patients (21%), respectively.

A total of 114 patients were divided into 3 groups in relation to the proportion of BAC component: 0% to 20% (n = 40), 21% to 50% (n = 38), and 51% to 100% (n = 36). Table 1 also shows the background factors and pathologic findings of these groups. Although patient distribution by age did not differ ($P = .2927$), there were significant differences among the groups with respect to sex ($P = .0001$), pathologic stage ($P = .0011$), T factor ($P = .0035$), N factor ($P = .0377$), P factor ($P = .0003$), Ly factor ($P = .0015$), and V factor ($P = .0002$). Male gender, advanced pathologic stage, larger tumor size, nodal involvement, pleural invasion, lymphatic invasion, and vascular invasion were

TABLE 2. Multivariate analysis of clinicopathologic factors for positive predictive values of pathologic nodal status

Factors	Odds ratio	95% CI	*P* value
Model 1 (R^2 = 0.236)			
Age	0.998	0.934-1.066	.9424
Sex	2.027	0.585-7.020	.2648
Size	1.205	1.063-1.366	.0036
Pathologic BAC	0.959	0.927-0.992	.0150
Model 2 (R^2 = 0.190)			
Age	0.999	0.938-1.065	.9847
Sex	1.503	0.466-4.843	.4948
Size	1.195	1.065-1.340	.0024
GGO on CT	0.960	0.916-1.006	.0857
Model 3 (R^2 = 0.231)			
Age	0.993	0.929-1.061	.8267
Sex	1.637	0.493-5.438	.4213
Size	1.200	1.061-1.357	.0037
TDR	0.963	0.935-0.993	.0145

CI, Confidence interval; R^2, determination coefficient; *BAC,* bronchioloalveolar carcinoma; *GGO,* ground-glass opacity; *TDR,* tumor disappearance rate.

observed more frequently among patients with a smaller proportion of BAC.

Next, to determine the independent predictors for pathologic nodal status, we performed a multivariate analysis. The tumor size was significant in all multivariable models, but age and gender were not significant in any model (Table 2). TDR ($R^2 = 0.231$, $P = .0145$) and BAC components ($R^2 = 0.236$, $P = .0150$) were found to be more clinically useful predictors of pN0 disease than GGO ratio ($R^2 = 0.190$), because their determination coefficients and levels of significance were high. A marginal but not significant correlation was found between GGO ratio and nodal status ($P = .0857$).

We performed logistic regression analyses to investigate which radiographic parameter correlated better with a pathologic BAC percentage: TDR or GGO ratio (Figure 1). A positive and significant correlation was found between pathologic BAC versus TDR ($R^2 = 0.727$, $P < .0001$) and GGO ratios ($R^2 = 0.488$, $P < .0001$). These data demonstrated that both TDR and GGO ratios obtained preoperatively from CT were well associated with BAC ratios obtained postoperatively from sections of the specimen and that TDR had a stronger impact as a predictor of pathologic BAC.

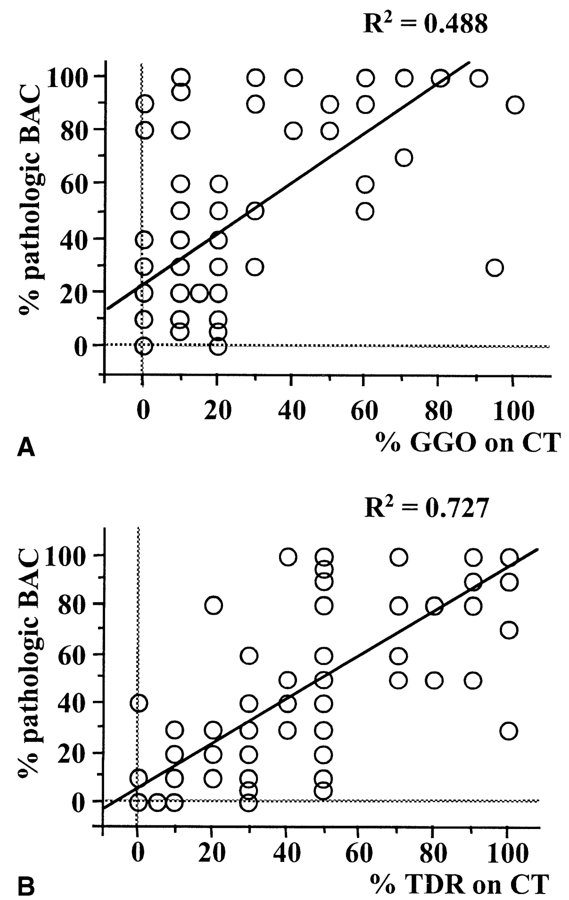

Figure 1. Regression parameters of radiographic findings and pathologic results. A, Correlation of radiographic GGO ratio and pathologic BAC ratio (R^2 = 0.488, *P* < .0001). B, Correlation of radiographic TDR ratio and pathologic BAC ratio (R^2 = 0.727, *P* < .0001). *BAC,* Bronchioloalveolar carcinoma; *CT,* computed tomography, *GGO,* ground-glass opacity; *TDR,* tumor shadow disappearance rate.

Discussion

The recent technologic improvement and extensive use of CT scanning for mass screening allow us to choose among various surgical options to treat small-sized lung cancers, especially adenocarcinomas. We have had great doubts about whether lobectomy, generally accepted as the standard cure for primary lung cancer, is compulsory for managing these small lesions.[17] There are, however, no accurate preoperative indicators of the biologic behavior of a tumor except for tumor size, location, and histology. Choosing lesser pulmonary resections instead of standard lobectomies requires better preoperative methods to distinguish advanced, aggressive cancers from early, indolent cancers. Patient selection is not easy because lymph node metastases are not exceptional in patients with small peripheral adenocarcinomas. Our data showed that among 114 patients with an adenocarcinoma 3 cm or smaller in diameter, 16 (14%) had nodal metastases and 22 (19%) had advanced-stage diseases. The remainder had a tumor that was not biologically aggressive.

Investigators have demonstrated that the degree of BAC component may reflect clinicopathologic and prognostic

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characteristics in patients with a small adenocarcinoma.[11,12] In the present study, lung adenocarcinomas accompanied by a higher BAC component showed a more indolent biologic behavior, and the proportion of BAC component on sections of surgical specimens was a significant independent predictor for nodal status. However, because the BAC area can only be defined after surgery, CT characteristics are watched with keen interest to choose surgical approaches preoperatively.

The proportion of GGO on HRCT was associated with the tumor biology and subsequently with the risk for nodal metastases and survival.[8-10,18] Matsuguma and colleagues[10] reported that all the cancers 2 cm or less in which the proportion of GGO was 50% or greater were BACs without nodal involvement and did not recur after resection. In addition, Takamochi and associates[15] proposed TDR as a predictor of the nodal status in patients with lung adenocarcinomas. In general, characterizing and quantifying CT findings used to be relatively subjective and based on visual estimation by individuals, possibly resulting in much discrepancy among the observers. Certainly, the lesions and parts indicating GGO or TDR on CT are not always BAC.[9,19] Therefore, we analyzed the correlation between the pathologic BAC ratio versus radiographic TDR or GGO ratio in small-sized adenocarcinomas 3 cm or less in diameter, which was one of the most crucial analyses in this study. The extent of both TDR and GGO area correlated well with that of BAC growth of adenocarcinomas. It must be emphasized that TDR, rather than GGO ratio, had an even more positive correlation with BAC proportion. In a multivariable analysis, TDR was considered an informative predictor of pathologic nodal status independent of age, sex, and tumor size. These findings can become an essential factor in planning proper management, in particular less invasive surgery for patients with a small adenocarcinoma. Although there were few patients in whom the BAC proportion was overestimated as TDR, BAC proportion was underestimated as TDR in some cases. The underestimation may have occurred because tumor cells induced mucous change at the alveoli and inflammatory cells infiltrated the alveolar lumens. Because patients with lower TDR are not often chosen for a lesser resection, the underestimation could be bypassed in the actual process of surgical intervention.

TDR is a reliable indicator of BAC and can serve to predict the biologic behavior of the tumor. This may be useful in identifying patients for lesser pulmonary resections.

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